PHOTOBIOLOGY/PHOTOMEDICINE

Milestones in Photocarcinogenesis

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It is currently estimated that over three million new nonmelanoma skin cancers will be diagnosed in the United States this year (Rogers *et al.*, 2010). The large majority is caused by chronic excessive exposure to UVR. Because of its public health relevance and the need to understand the biologic impact of UVR on the skin, there has been a long-standing interest in the mechanisms by which this form of radiant energy causes skin cancer. Observations from this line of investigation have led to a better understanding of UV-induced skin cancer specifically and, more broadly, of cancer in general. The concept of multistage carcinogenesis, the influence of various signal transduction pathways in cancer development, the relationship of oncogenes and tumor suppressor genes to cancer, the contribution of DNA damage and its repair to carcinogenesis, the participation of the immune system in tumorigenesis, and the identification of new chemopreventive and therapeutic agents have all benefited from observations about UVR-induced skin cancer.

UVR AND NONMELANOMA SKIN CANCER

The notion that chronic sun exposure might be a cause of nonmelanoma skin cancer was first described in 1894 when Unna (1894) reported that sailors, who were chronically exposed to large amounts of sunlight, were predisposed to developing skin cancers, primarily located on sun-exposed areas of skin. Further characterization of the photobiologic aspects relied largely on experimental animal models. Using mice, Findlay (1928) was the first to show that chronic exposure to UVR from an artificial light source could cause squamous cell carcinomas (SCCs). Decades later, Blum (1959) showed that interposition of plate glass, which selectively blocks UVB wavelengths, between the light source and the animals being irradiated greatly reduced skin tumor incidence, indicating that UVB was much more potent at causing these malignancies than UVA. Further characterization of the wavelength dependence of UV carcinogenesis revealed a 10-fold decline in tumor production between 300 and 310 nm and a 70-fold reduction in tumor incidence between 310 and 320 nm (Freeman, 1975). The animal model developed by Findlay (1928), however, failed to produce basal cell carcinomas (BCCs), an accomplishment that was not achieved until mutant mice genetically deficient in the *PTCH* gene were chronically exposed to UVR (Aszterbaum *et al.*, 1999). It is important to note that wavelengths within the UVA have also been shown to cause skin cancers, but, on a per photon basis, require much larger amounts of UVA radiation and longer lengths of time to develop (Strickland, 1986; Sterenborg and van der Leun, 1990). However, when combined with psoralens used in clinical practice for the phototherapy of psoriasis and other skin diseases (Stern *et al.*, 1984) and other medications (O'Donovan *et al.*, 2005; Cowen *et al.*, 2010), UVA can be a much more potent carcinogen.

DNA DAMAGE AND ITS REPAIR

The similarity between the wavelengths responsible for nonmelanoma skin cancer (NMSC) and the action spectrum for DNA damage led to the conclusion that DNA damage might, at least in part, be responsible for the carcinogenic effects of UVR (Setlow and Setlow, 1962). Aside from the observation that the presumed action spectrum for photocarcinogenesis is similar to that for DNA damage, several other lines of evidence lend credence to the theory that DNA is a relevant target for UVR, as it relates to UV-induced NMSC. Much of this derives from studies in the cells of individuals with the genetic disease xeroderma pigmentosum and from experiments conducted in genetically engineered mice with mutations similar to those observed in xeroderma pigmentosum (de Vries *et al.*, 1995). These patients are predisposed to actinically damaged skin and NMSC, and they develop melanomas at an unusually young age. Cleaver (1968, 1969) was the first to show that these patients have a defect in the repair of UV-damaged DNA. Following exposure to UVR, cell lines derived from these patients have more mutations and greater amounts of cell death and chromosomal DNA damage than those from normal individuals (Cleaver, 1968, 1969). Xeroderma pigmentosum can be caused by mutations in several genes, all of which are important in the DNA repair pathway.

UVR produces multiple types of DNA damage, including single-strand breaks, pyrimidine dimers, purine photoproducts, DNA–protein cross-links, and (6-4) photoproducts, but the greatest interest with respect to UV carcinogenesis has been in cyclobutane pyrimidine dimers, which are

the major DNA photoproduct formed following UVR and which are repaired in human skin primarily by nucleotide excision repair. Cytosine to thymine (C to T) mutations when two pyrimidines lie next to each other—or, at times, CC to TT mutations—are characteristic of UV damage and are not caused by other mutagens; as such, these signature mutations have been used to identify UV-induced DNA damage (Brash *et al.*, 1991).

STAGES OF PHOTOCARCINOGENESIS

The concept that cancer development is a multistage process, in which molecular and biochemical changes accumulate in target cells in an orderly sequence of events, originated in polyaromatic hydrocarbon skin carcinogenesis. During the initiation stage, DNA damage occurs that produces inactivating mutations in selected tumor suppressor genes or activating mutations in oncogenes. These mutant keratinocytes are not clinically apparent, but they undergo additional biochemical changes in the promotion stage that result in visible premalignant papillomas. Of all the premalignant papillomas, a small proportion acquire further alterations that allow them to become invasive carcinomas. Epstein was able to show in mice that this same process also occurs during photocarcinogenesis, and that UVR can serve as both a tumor initiator creating mutations and a tumor promoter producing other biochemical effects (Epstein and Epstein, 1962; Epstein and Roth, 1968).

UV AND TUMOR INITIATION

During the initiation stage, UV-induced DNA damage produces mutations in target keratinocytes. Those that result in alterations in the p53 tumor suppressor gene are found in both basal cell and SCCs. Those that occur in the sonic hedgehog pathway are critical for producing BCCs. The importance of the sonic hedgehog pathway as an initiating mutation in BCCs was first recognized when it was observed that *PTCH* gene mutations were present in patients with basal cell nevus syndrome (Johnson *et al.*, 1996), an autosomal dominant disorder in which patients develop large numbers of BCCs. The *PTCH* gene is an essential component of the sonic hedgehog signaling pathway. In the skin, the sonic hedgehog pathway is important for epidermal stem cell regulation, the generation of sebaceous glands, and hair follicle development. Studies have shown that mutations in the *PTCH* gene, as well as other genes in the sonic hedgehog pathway, are present in most BCCs. Many of the mutations in this pathway contain UV signature lesions (Gailani *et al.*, 1996; Couve-Privat *et al.*, 2002). These findings in humans have been corroborated in mouse models in which the sonic hedgehog pathway is dysregulated (Athar *et al.*, 2004).

Mutations in p53 have been detected in nearly 60% of cutaneous SCCs (Brash *et al.*, 1991) and up to half of BCCs (Zhang *et al.*, 2001). p53 has many biological activities. It has been shown to activate DNA repair enzymes, cause cell cycle arrest, and induce apoptosis, all of which retard photocarcinogenesis; UV-induced p53 mutations impair those functions (Ziegler *et al.*, 1994; Berg *et al.*, 1996). Restoration of mutant p53 to a functional form of the protein has been shown to inhibit UVB-induced skin tumorigenesis in susceptible animal models (Tang *et al.*, 2007).

UV AND TUMOR PROMOTION AND PROGRESSION

Many of the biochemical changes that occur during the promotion stage of UV carcinogenesis occur in response to reactive oxygen intermediates. In animal models, it has been shown that a variety of antioxidants present in dietary products—green tea (Wang *et al.*, 1991), grape seed extract (Sharma and Katiyar, 2010), silymarin (Katiyar, 2002)—can suppress UV-induced skin cancer formation in animal models.

Another target of UVR is the enzyme ornithine decarboxylase (ODC). ODC is the rate-limiting step in polyamine synthesis, which is involved in cell proliferation. ODC activity is increased following acute UV exposure, and chronic exposure results in increased basal levels of the enzyme (Lowe *et al.*, 1978; Hillebrand *et al.*, 1990). BCCs and SCCs can be prevented in PTCH1$^{+/-}$ mice by inhibiting ODC (Tang *et al.*, 2004).

An additional biochemical change that occurs during the promotion and progression stages of UV carcinogenesis is increased expression of the enzyme cyclooxygenase-2 (COX-2). COX-2 is not constitutively expressed in normal epidermis, but its synthesis is increased markedly following UVR exposure. It can be easily detected in actinic keratoses (AKs), SCCs, and BCCs (Fischer *et al.*, 1999; An *et al.*, 2002). COX-2 is an enzyme required for the formation of prostaglandin E2 from arachidonic acid. Prostaglandin E2 has been associated with a broad range of processes implicated in UV-induced tumor promotion and progression, including inflammation, epithelial to mesenchymal transition, angiogenesis, and immunosuppression. COX-2 inhibitors have been successful at preventing UV-induced skin cancers in animal models (Fischer *et al.*, 1999; Pentland *et al.*, 1999; An *et al.*, 2002). Epidemiological studies have also shown that individuals who regularly take nonsteroidal anti-inflammatory drugs have a lower incidence of cutaneous SCCs than those who do not (Butler *et al.*, 2005).

IMMUNOLOGY OF PHOTOCARCINOGENESIS

The skin tumors that develop following chronic UV exposure are highly antigenic in mice and in humans. Immunosuppressive medications used to treat organ transplant recipients greatly increase the likelihood of UV-induced skin cancers, and, in addition, these cancers are more aggressive than those observed in the general population (Hoxtell *et al.*, 1977; Hartevelt *et al.*, 1990). In spite of the immunogenicity of UV-induced skin tumors, they evade the host immune defenses that have evolved to eliminate neoplastic cells before they become invasive malignancies (Kripke, 1974). This seeming contradiction was resolved in a series of experiments in which UV-induced tumors were transplanted to syngeneic mice. When

the tumors were transplanted to mice that had not received any UV exposure, they initially grew but then regressed once host immune defenses were activated. In contrast, when the same tumors were transplanted to syngeneic mice that had been exposed to subcarcinogenic amounts of UVR, they grew progressively and eventually killed the recipients. The conclusion from this study was that in addition to producing mutations in skin cells UVR impairs host immune responses that are responsible for their eradication before they can develop into clinically apparent tumors. UVR, which only reaches the superficial dermis, was found to produce these effects by perturbing the function of antigen-presenting cells in the skin, stimulating the production of regulatory T cells and augmenting the production of the immunosuppressive cytokine IL-10, while at the same time diminishing the production of IL-12 (Toews *et al.*, 1980; Elmets *et al.*, 1983; Schwarz *et al.*, 1996; Shreeder *et al.*, 1998; Loser *et al.*, 2007). The clinical relevance of the importance of the immune system in UVR-induced skin cancers was supported by observations in humans. Individuals who developed suppressed immune responses following UVR were found to be significantly more likely to develop NMSC than those who were resistant to its immunosuppressive effects (Yoshikawa *et al.*, 1990; Cooper *et al.*, 1992).

CLINICAL RELEVANCE OF PHOTOCARCINOGENESIS RESEARCH

Research identifying the mechanisms by which UVR causes skin cancer have served as the basis for new methods by which NMSC can be prevented. The use of sunscreens is recommended by most physicians for the prevention of skin cancer, although they are not specifically approved by the US Food and Drug Administration for that purpose. There are published data to indicate that their regular application will reduce the incidence of AKs and cutaneous SCCs. In subjects who previously have had AKs, sunscreens were observed to diminish the incidence of new AKs over a 7-month period of time (Thompson *et al.*, 1993). Sunscreens have also been found to produce a 35% reduction in cutaneous SCCs (Green *et al.*, 1999). There are no studies achieving statistical significance that have shown that sunscreens prevent BCCs, although there is a trend in that direction in one long-term follow-up study (van der Pols *et al.*, 2006).

T4 endonuclease V is a bacterial DNA repair enzyme that removes cyclobutane pyrimidine dimers through base excision repair, thereby helping to prevent mutations in UV-irradiated keratinocytes. This agent has been found to reduce the incidence of AKs and BCCs in xeroderma pigmentosum patients (Yarosh *et al.*, 2001).

GDC-0449 is an oral small-molecule inhibitor that selectively interrupts activation of downstream hedgehog genes, which, as was mentioned, is important for the development of sporadic BCCs and BCCs in basal cell nevus syndrome. This molecule is an effective treatment for locally advanced and metastatic BCC (Von Hoff *et al.*, 2009), and it causes regression and prevention of BCCs in the basal cell nevus syndrome (Tang *et al.*, 2012).

Difluoromethylornithine, an agent that irreversibly inhibits ODC, has been shown to act on the promotion and early progression of UV-induced skin tumorigenesis in animal models (Tang *et al.*, 2004). In a skin cancer prevention study of 291 participants for 4 to 5 years, there was a statistically significant 33% reduction in the development of new BCCs in patients treated with difluoromethylornithine compared with placebo subjects (Bailey *et al.*, 2010).

Celecoxib is an oral medication that inhibits COX-2 activity. In a multicenter, double-blind, randomized phase II/III trial of 240 patients, celecoxib was shown to reduce the number of new BCC and SCC by up to 60% over an 11-month period of time (Elmets *et al.*, 2010). In another trial, when celecoxib was administered over a 24-month period of time with a follow-up interval of 36 months, there was a significant reduction of new BCCs in patients with the basal cell nevus syndrome, who at the initiation of the study had less than 15 BCCs (Tang *et al.*, 2010).

Retinoids promote differentiation, growth arrest, and apoptosis of epidermal keratinocytes. These agents have been found to be effective chemopreventive agents for NMSC in high-risk individuals, including xeroderma pigmentosum patients (Kraemer *et al.*, 1988), organ transplant recipients (Bavinck *et al.*, 1995), and those having received large numbers of psoralen photochemotherapy treatments (Nijsten and Stern, 2003).

Finally, high-fat diets increase inflammation, which is known to promote UV-induced skin cancers, possibly by augmenting the synthesis of tumor-promoting prostaglandins. A randomized, controlled clinical trial found that those individuals with reduced dietary fat intake developed significantly fewer new AKs and NMSCs than those in whom dietary fat intake was comparable to a normal diet (Black *et al.*, 1994).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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